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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David BERD

Serial No.: 08/203,004 Art Unit: 1642

Confirmation No.: 2699

Filed: February 28, 1994 Examiner: Susan UNGAR

For: COMPOSITION AND METHOD OF USING TUMOR CELLS

SUPPLEMENTAL BRIEF ON APPEAL

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

August 28, 2006

Sir:

This Supplemental Brief on Appeal is submitted in response to the Examiner's Office Action mailed May 26, 2006, along with a Petition for a two-month extension of time and authorization to charge the appropriate fee. A first Brief on Appeal was filed on December 28, 2001 together with a Petition for a five-month extension of time and the appropriate fee, following the Notice of Appeal filed May 29, 2001 and the response to the Final Office Action mailed on November 29, 2000. A second Brief on Appeal was filed on April 8, 2002. It is believed that no additional fees are required for these submissions. However, should it be determined that additional fees are required or that any refund is due in connection with this application, the Commissioner is hereby authorized to charge the required fee(s) and/or credit the refund(s) due to Deposit Account No. 50-0310.

This Brief addresses the Examiner's concerns cited in the Action dated May 26, 2006. Specifically, this Brief (i) identifies the real party in interest; (ii) provides a double-spaced Appendix; (iii) provides the status of all claims in the application; and (iv) states the issues presented for review in accordance with 37 C.F.R. 1.192(c)(6). Since this is a Supplemental Brief, the Exhibits referenced herein are not included with this Brief, as they were filed with the previous Brief on Appeal in April 2002 and are identical to those Exhibits.

1. The Real Party in Interest

Thomas Jefferson University (TJU), Philadelphia, Pennsylvania, is the assignee of this application. Avax Technologies, Inc., of Overland Park, Kansas (Avax), has an exclusive license from TJU. Accordingly, Avax and TJU are the real parties in interest.

2. Related Appeals and Interferences

There are no related appeals or interferences.

3. Status of Claims

Claims 43, 44, 47, 49-62, 64-72, and 74-77 are pending and the final rejection of all of these claims is the subject of this Brief. Claims 1-42, 45, 46, 48, 63, and 73 have been cancelled in previously filed Responses to Office Actions during the prosecution of this application. A copy of the pending claims is attached as an Appendix immediately following this Brief.

4. Status of Amendments

Appellant filed an amendment May 29, 2001 in response to the Final Office Action dated November 29, 2000. The Examiner entered this amendment pursuant to the Advisory Action dated July 5, 2001 (copy attached as Exhibit 1).

5. Summary of the Invention

The present invention concerns a composition comprising human tumor cells (other than melanoma cells) conjugated with a hapten.[1] (Specification, page 8, lines 4-6; page 15, lines 4-9). Such haptenized tumor cells have been surprisingly and unexpectedly discovered to form an effective immunogenic component in a vaccine composition for immunotherapy of cancer of the type from which the cells were derived. (Specification, page 11, line 26 to page 12, line 1; page 17, lines 6-16). The haptenized tumor cells are prepared from tumor cells retrieved from the patient receiving treatment (i.e., they are "autologous"), and are haptenized and rendered incapable of growing in the body of a human before injection therein. (Specification, page 12, lines 1-5 and 19-22; page 15, line 26 to page 16, line 13).

In another aspect, the invention provides a method for treating a malignant tumor (other than melanoma) in a human patient by co-administering a composition comprising haptenized autologous human tumor cells, of the same tumor type as the tumor in the patient, with an adjuvant. (Specification, page 8, lines 6-10; page 11, line 27 to page 12, line 5; page 14, lines 3-20; page 15, line 20). The composition elicits at least one of the following responses upon

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[1] A hapten is a small molecule that, when conjugated to a carrier, can elicit a specific immune response. Preferred haptens include the highly reactive dinitrophenyl and trinitrophenyl groups. (Specification, page 15, lines 4-9).

administration to the patient with the adjuvant: an inflammatory immune response against the tumor of the patient; a delayed-type hypersensitivity response against the tumor of the patient; and activated T lymphocytes that infiltrate the tumor of the patient. (Specification, page 17, lines 6-13; page 18, lines 6-13).

In a further aspect, the invention provides a method for treating a malignant tumor in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the patient, along with an adjuvant, at least six times. (Specification, page 14, lines 7-18 and 25-26; page 22, lines 22-26). In still a further embodiment, the patient is given a dose of cyclophosphamide prior to the first administration of the composition. (Specification, page 21, lines 23-25).

The composition of the invention represents an advance over prior experiments involving haptenization of tumor and other cells for testing in animal models. (Specification, page 17, lines 3-16). Prior art experiments suggested that haptenization results in hapten-specific immunity and, in certain experimental animal models, could elicit immunity to unmodified cells as well. (Specification, page 2, line 25 to page 4, line 28). However, the model systems left unresolved whether a human therapy was possible, as hapten-specific immunity would not be useful against metastasized tumor cells or tumor cells remaining after tumor resection, because the residual tumor cells in a patient do not bear hapten.

The invention addresses a need in the art for an effective immunotherapy for tumors, especially non-melanoma tumors. (Specification, page 11, lines 21-25). Administering haptenized tumor cells unexpectedly increases the effectiveness of the resulting tumor-specific immune response, especially with six or more immunizations, resulting in a more effective

immunotherapy. (Specification, page 22, lines 25-26). Most importantly, the inventor has discovered that the protective immunity is not hapten-specific, which the prior art suggested would be the case. (Specification, page 17, lines 3-16; page 23, lines 9-11).

6. Issues

The following issues are presented on appeal[2]:

(i) Whether claims 47, 65-72 and 74-77 are obvious (see paragraph No. 5 of the Final Office Action [Exhibit 2], referencing Paper No. 41 [Exhibit 31, Section 5, pages 2-3 and Paper No. 36 [Exhibit 4], Section 10, pages 8-12) over Murphy et al. (Lab Invest 1990;62:70A; hereinafter "Murphy" [Exhibit 5]), in view of U.S. Patent No. 5,702,704 (hereinafter `704 patent" [Exhibit 6]), U.S. Patent No. 5,626,843 (hereinafter "'843 patent" [Exhibit 7]), U.S. Patent No. 5,008,183 (hereinafter "'183 patent" [Exhibit 8]), or U.S. Patent No. 4,232,001 (hereinafter "'001 patent" [Exhibit 9]); Berd et al., (Proc AACR 1989:30:382; hereinafter "Berd 1989" [Exhibit 10]), and Geczy et al. (J Immunol. 1970;19:189-203, hereinafter "Geczy" [Exhibit 11]).

(ii) Whether claims 47, 65-72, and 74-77 are obvious over Berd 1989 in view of the 704 Patent, the '843 Patent, the 183 Patent, or the '001 Patent, and further in view

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[2] The Examiner withdrew the rejection of claims 43, 49-51, and 54-55 for allegedly not being enabled by the disclosure in the Advisory Action (Exhibit 1) in view of the amendment of claim 43 to recite that the composition of the invention elicits, when administered together with an adjuvant, an immune response. In a previous Office Action, the Examiner stated that the specification enables a method for treating a malignant tumor in a human patient comprising administering the composition of claim 43 (i.e., haptenized autologous non-melanoma tumor cells) and BCG (Office Action dated April 28, 1999 [Exhibit 4; Paper No. 361, paragraph No. 6). The specification supports this recitation, e.g., Examples 2 and 3 report eliciting a striking inflammatory response when the composition of the invention was administered together with the adjuvant BCG. Claims 49-51 and 54-55 depend from claim 43.

of Geczy (see paragraph 6 of the Final Office Action [Exhibit 21, referencing Paper No. 41 [Exhibit 3], Section 6, page 4 and Paper No. 36 [Exhibit 41, Section 11 , pages 12-15).

(iii) Whether claims 43, 44, 47, 49-62, 64-72, and 74-77 are unpatentable over Berd '89 in view of the 704 Patent, the '843 Patent, the 183 Patent, or the '001 Patent; and Geczy, in further view of Wiseman et al. (West J Med 1989;151:283-288, hereinafter "Wiseman" [Exhibit 12]) (see paragraph 7 of the Final Office Action [Exhibit 2], referencing Paper No. 41 [Exhibit 3], Section 7, pages 4-5 and Paper No. 36 [Exhibit 4], Section 12, pages 15-18).

(iv) Whether claims 43, 44, 47, 49-62, 64-72, and 74-77 are unpatentable over Berd '89 in view of the '704 Patent, the '843 Patent, the '183 Patent, or the '001 Patent; and Geczy, in further view of Berd et al. (PASCO 1983;2:56, hereinafter "Berd 1983 [Exhibit 13]) (Final Office Action [Exhibit 2], paragraph No. 8, referencing Paper No. 41 [Exhibit 3], Section 8, page 6 and Paper No. 36 [Exhibit 4], Section 13, pages 18-21).

(v) Whether claims 43, 44, 47, 49-62, 64-72, and 74-77 are unpatentable over Berd 1989 in view of the '704 Patent, the '843 Patent, the 183 Patent, or the '001 Patent; and Geczy, in further view of Sanda et al. (J Cellular Biochem 1 993;suppl. 1 7D: 120, hereinafter "Sanda" [Exhibit 14]) and Moody et al. (J Urol 1991;145:293A, hereinafter "Moody" [Exhibit 15]) (Final Office Action [Exhibit 2], paragraph No. 9, referencing Paper No. 41 [Exhibit 3], Section 9, page 7 and Paper No. 36 [Exhibit 4], Section 14, pages 21-25).

7. Grouping of Claims

The claims do not stand or fall together. In this section, three groups of claims, designated Group A-C, with distinct patentability considerations are identified. In section 8

below, Appellant describes why the claims in Groups A-C are believed to be separately patentable.

Group A: Claims 43 and 49-55. These claims are directed to compositions that have distinct features and patentability considerations. Within this group, claim 49 is directed to a Markush group of tumors that has distinct patentability considerations relative to the genus of tumors. In addition, claim 51 is directed to a specifically recited hapten.

Group B: Claims 44, 56-62, 64, and 76. These claims are directed to a method for treating a malignant tumor in a human, which has distinct patentability considerations relative to the composition claims. Within this group, claims 56 and 57 are directed to a Markush group of tumors that has distinct patentability considerations relative to the genus of tumors. In addition, claim 59 is directed to a specifically recited hapten.

Group C: Claims 47, 65-72, 74, 75, and 77. These claims are directed to a method for treating a malignant tumor in a human, which has distinct patentability considerations relative to the composition claims and to the other method of treatment claims because these claims (i) do not exclude treatment of melanoma tumors and (ii) require at least six administrations of the immunotherapy vaccine. The Examiner has rejected these claims for different reasons than the other claims, which further establishes that these claims stand or fall separately from the other claims.

Within this group, claims 65 and 66 are directed to a Markush group of tumors that has distinct patentability considerations relative to the genus of tumors. In addition, claim 68

is directed to a specifically recited hapten. Finally, claim 70 recites a specific regiment for administration of cyclophosphamide (CY).

8. Argument

The first part of this section summarizes the rejections as they pertain to each claim group, and some general considerations that are important to all issues raised in the Final Office Action. The second part of this section discusses each issue (i.e., obviousness rejection) separately, explaining why each claim group involved in the same rejection, where applicable, is believed to be separately patentable.

Table 1. Rejected Claims and Cited References

No.	Reference Cited in Resection	Rejected Claims		
		Group A	**Group B**	**Group C**
a	Murphy in view of Antibody Patents,* Berd 1989, and Geczy		76	47,65-72, 74-75, 77
b	Berd 1989 in view of Antibody Patents* and Geczy		76	47, 65-72, 74-75, 77
c	Berd 1989 in view of Antibody Patents,* Geczy, and Wiseman	43, 49-55	44, 56-62, 64, 76	47, 65-72, 74-75, 77
d	Berd 1989 in view of Antibody Patents,* Geczy, and Berd	43, 49-55	44, 56-62, 64,76	47, 65-72, 74-75, 77
e	Berd 1989 in view of Antibody Patents,* Geczy, Sanda and Moody	43, 49-55	44, 56-62, 64,76	47, 65-72, 74-75, 77

* "Antibody Patents" = '704, '843, '183, and '001 Patents

The relevant test for obviousness requires three basic factual inquiries: the scope and content of the prior art are to be determined; the differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the art resolved. *Graham v. Deere*, 383 U.S. 1, 17 (1966); *Ruiz v. A.B. Chance Co.*, 57 USPQ2d 1161, 1165 (Fed. Cir. 2000). The relevant inquiry involves three steps. First, there must be some suggestion or motivation to modify what is taught in a reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference or combination of references must teach all of the claim limitations. Both the motivation and the reasonable expectation of success must be found in the prior art, not in appellant's disclosure. *See*, MPEP § 2143, *citing In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As explained in detail below, the Final Office Action fails to establish a *prima facie* case for obviousness under these requirements because there is no motivation to combine the references, and, even when forcibly combined, they do not provide a reasonable expectation of success.

In all of the rejections, the Examiner relies on the Berd 1989 abstract as an allegedly successful example of treatment of melanoma by administration of DNP-conjugated autologous melanoma cells in connection with BCG and a preceding dose of cyclophosphamide. The Examiner also contends that it would have been expected that the autologous irradiated melanoma, lung, colon, kidney, and colon cancer cells of Wiseman ([Exhibit 111 discussed below) would be successfully substituted for the melanoma cells of Berd 1989 to treat other cancer types (Final Office Action [Exhibit 2], bridging paragraph between pp. 5 and 6).

However, both of these conclusions depend on according more weight to the Abstract than one of ordinary skill at the time of the invention would have given it.

To factually determine what a reference teaches one of ordinary skill in the art in implementing the Graham standard, the courts have relied upon affidavit evidence either by experts or those of ordinary skill in the art. *See In re Carroll* 202 USPQ 571 (CCPA 1979); *In re Piasecki*, 223 USPQ 785, 789 (Fed. Cir. 1984); *In re Oelrich*, 198 USPQ 210 (CCPA 1978). Furthermore, affidavits of those skilled in the art have been held to constitute factual evidence of the level of skill in the art. *E.g., In re Piasecki*, 223 USPQ at 789; *In re Oelrich*, 198 USPQ 210, 214-15. Such affidavits constitute competent evidence that cannot be ignored. *See e.g., Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 227 USPQ 657, 674-75 (Fed. Cir. 1985).

Appellant has therefore addressed the teachings of this reference through the lense of one of ordinary skill in the art, Dr. Donald Braun, who attended an interview with the Examiner and her supervisor on January 5, 2000.[3] As set forth by the Braun Declaration [Exhibit 16] accompanying the response to the Final Office Action[4], Berd 1989 does not describe a successful immunotherapy for melanoma (Braun Declaration, paragraph 7). On the contrary, it represents a preliminary result that raises more questions and ambiguities than it answers. Early

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[3] Dr. Donald Braun has a long career in the field of immunological oncology, as evidence by his *curriculum vitae*, attached as Exhibit A to the Braun Declaration [Exhibit 16]. There can be no doubt as to his qualifications as one of at least ordinary skill in the art.

[4] The Braun Declaration memorializes comments made by Dr. Braun during the personal interview with the Examiner and her Supervisor on January 5, 2001, at which this application and a number of related applications by the same inventor were discussed. The points made therein reinforce scientific and factual argument distinguishing the prior art of record already made by applications. The Examiner agreed at the interview that Dr. Braun's Declaration would substantiate these points. However, for reasons unknown to the Appellant, the Examiner stated in the Advisory Action (Exhibit 1) that she had not considered the Braun Declaration "... because Applicant has not shown good and sufficient reasons why it was not earlier presented..." (Advisory Action [Exhibit 11, page 2). It had seemed self-evident that presentation of this Declaration could not have preceded the clarification of issues achieved at the interview.

animal work on tumor immunotherapy could not establish whether similar approaches could work in humans (Braun Declaration, paragraph 8). The Abstract fails to provide a definitive protocol that would permit one to repeat the work, determine whether this approach elicited an immune response to unmodified cells, or establish that it achieved any clinical benefit (Braun Declaration, ¶¶ 9, 10, 11).

Thus, since the primary reference, Berd 1989, fails to provide any expectation of success, *i.e.*, clinical benefit, using the haptenized tumor cell approach in melanoma patients, this reference is completely irrelevant in providing any expectation of success for such an approach in other types of cancer. Since no other reference cited by the Examiner makes up for this fundamental flaw, nor the combination of them (see below), obviousness does not obtain.

With these considerations in mind, we turn to each issue, and the specific grounds for rejection.

a. The Rejection of Claims 47, 65-72, and 74-77 over Murphy in view of '704 Patent, '843 Patent, '183 Patent, or '001 Patent; Berd 1989; and Geczy

The rejected claims are all part of Group C, except for claim 76, which is part of Group B. Claim 76 is directed to a method for treating a non-melanoma malignant tumor in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the patient, with an adjuvant. The broadest claim of Group C, claim 47, is directed to a method for treating a malignant tumor in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the patient, along with an adjuvant, at least six times. As disclosed in Examples 3, 4, and 6 of the instant application, administration of the

immunotherapeutic vaccine comprising haptenized tumor cells on at least six, and in most cases eight, occasions resulted in actual treatment of tumors, with statistically significant greater cancer-free survival compared to controls (who received non-haptenized vaccine) at two years. (Specification, page 29, lines 22-25). The difference was highly significant. (Id., page 30, lines 26-27; page 41, line 24 to page 42, line 8).

i. The Examiner's Reasoning

The Examiner states that Murphy teaches a method for treating melanoma comprising sensitizing with DNCB, administering a therapeutically effective amount of cyclophosphamide (CY), and administering a therapeutically effective amount of autologous, irradiated DNP-conjugated melanoma cells mixed with BCG adjuvant. The Examiner notes that Murphy does not teach administration of at least six vaccine doses at spaced intervals, a specific dose of CY (300 mg/M2), prior sensitization with 1 -fluoro-2,4-dinitrobenzene, or eliciting certain specified immune responses against the tumor. The Examiner cites the '704, '843, '183, and '001 Patents for teaching administration of at least six doses of antigen; Berd 1989 for teaching a successful method of treating melanoma with the specified dosage of CY using DNP-conjugated melanoma cells, and Geczy for teaching halogenated dinitrobenzenes for eliciting delayed type hypersensitivity. (Paper 36 [Exhibit 4], pages 9-10). The thrust of this rejection, then, is that it would have been obvious from the combined teachings of Murphy; the '704, '843, 183, or '001 Patents; and Berd 1989 to administer at least six doses of a haptentized tumor cell vaccine, and that various haptenization reagents can be used as described by Geczy.

Appellant have previously argued that the references cannot be combined as suggested by the Examiner without employing impermissible hindsight from the disclosure of

the invention. The Examiner contends that "[s]ome degree of hindsight is permissible in making rejections under 35 U.S.C. 103 since it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning." (Final Office Action [Exhibit 2], page 3).

ii. Appellant's arguments

The teachings of ***Berd 1989*** has been discussed above and in the Braun Declaration [Exhibit 161, noting in particular the lack of guidance and expectation of success of this reference.

As noted in Appellant's amendment filed September 22, 2000 on page 14, paragraph 3.d, ***Murphy's*** teachings are cumulative to those of Berd 1989 in all aspects relied upon by the Examiner, thereby suffering from the same lack of guidance and expectation of success for the haptenized-tumor-cell approach in melanoma, and, of course, even more so in the case of non-melanoma tumors.

The teachings and deficiencies of ***Geczy*** have been discussed in Appellant's amendment filed September 22, 2000, on pages 11 -12, paragraphs 3.b.iii. Geczy proposes that direct haptenization of lymphocytes is necessary for lymphocyte transformation, thereby primarily relating to anti-hapten responses. Geczy does not pertain to cancer therapy. In addition, Geczy's anti-hapten responses would not be useful for tumor treatment, since they would attack the haptenized tumor cell vaccine itself instead of residual tumor cells. Thus, to the extent that the teachings of Geczy relate to those of Berd 1989 and/or Murphy, they diverge and teach away from using haptens to elicit a protective immune response against unmodified tumor cells.

With respect to the *'704, '843, '183, and '001* Patents, their teachings and deficiencies were also discussed in the amendment dated September 22, 2000, pages 10-11 , paragraph 3.b.ii. Since the teachings of these patents are substantially overlapping, they are hereinafter collectively referred to as the "Antibody Patents."

The immunization schedules proposed in the Antibody Patents result in the generation of antibodies against the antigens. Such antibodies can be useful as diagnostic reagents, but since the subjects do not develop protective immunity to the immunogen(and are not intended to do so), the Antibody Patents are irrelevant for immunotherapy treatment regimes. In fact, the Antibody Patents fail to suggest, and indeed teach away from, generating an immune response to a carrier, since the goal of the references is to elicit an immune response to a "carried" substance, i.e., the antigen, and not a carrier.[5] This is directly analogous to eliciting an anti-hapten antibody response against a hapten "carried" by a tumor cell. As pointed out above, such a result would be contrary to the invention, since an anti-hapten immune response would not affect residual tumor cells remaining after resection or metastasis. Thus, the Antibody Patents, as well as Geczy, teach away from a key point of the invention; the elicitation of an immune response towards unmodified tumor cells (the "carriers").

Finally, the Antibody Patents do not teach or suggest at least six administrations or immunizations for the treatment of cancer. No objective teaching thus exists in these patents that would suggest to or motivate one of skill in the art to administer antigens or antibodies to humans at least six times at spaced intervals in order to treat cancer.

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[5] See, e.g., the '704 patent, column 13, line 38 to column 14, line 9.

In conclusion, there is no motivation to combine references that relate to immunotherapy of cancer and anti-tumor responses (Murphy, Berd 1989) with references which impliedly or explicitly teaches anti-hapten responses and do not even relate to cancer treatment (Geczy, Antibody Patents). Even when forcibly combined, however, there are no teachings about treatment of non-melanoma tumors, or about successful treatment of any tumor type, in this combination of references.

iii. Separate Patentability Issues

Claim 76 (Group B) cannot be obvious over the cited combination of references because (1) the references cannot be combined (see preceding section), and (2) the combination does not teach treatment of ***non-melanoma*** tumors, an explicit feature of the claim.

The claims of Group C cannot be obvious over the cited combination of references because (1) the references cannot be combined (see preceding section), and (2) even if forcibly combined, there would be no reasonable expectation that six or more administrations of vaccine would yield a more successful tumor treatment as demonstrated in the Examples. If anything, the combined teachings of the references leads one of ordinary skill to predict that six or more administrations of a haptenized tumor cell vaccine would yield a stronger anti-hapten antibody response, e.g., as shown by the Antibody Patents. Such an outcome leads away from the Group C claims in particular, as these claims all require at least six administrations of vaccine.

Thus, there are different reasons for the non-obviousness of claim 76 and the claims of Group C over the cited combination of references. In addition, claim 76 depends from

claim 44, which was not included by the Examiner in this rejection. Accordingly, claim 76 and Group C are separately patentable.

iv. *Errors in Rejection*

The Examiner has made a number of legal errors to arrive at a conclusion of obviousness based on the combined teachings of these references, primarily by failing to properly articulate the Graham factors. For example, Examiner did not properly consider the scope and content of the prior art, and the differences between the prior art and the claimed invention. *Ruiz*, 57 USPQ2d at 1167. The Examiner further failed to establish the level of ordinary skill in the art, *Id.* at 1168, which Appellant has established through the Braun Declaration as well as through the references cited by the Examiner.

With respect to considering the scope and content of the prior art and the differences between the prior art and the claimed invention, the Examiner failed to articulate "... a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." *Id.* at 1167, *citing In re Rouffet*, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) and *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). The Federal Circuit provides explicit guidance in *Ruiz* on the factual findings to make in determining a reason, suggestion, or motivation to combine:

> The reason, suggestion, or motivation to combine may be found explicitly or implicitly: 1) in the prior art references themselves; 2) in the knowledge of those of ordinary skill in the art that certain references, or disclosures in those references, are of special interest or importance in the field; or 3) from the nature of the problem to be solved, "leading inventors to look at references relating to possible solutions to that problem."

Id. (citations omitted). The Examiner merely alludes to a "conventional immunization scheduled" (Final Office Action [Exhibit 21, page 4; Paper 36 [Exhibit 4], page 11) without providing any basis for linking a conventional immunization schedule for eliciting diagnostic antibodies to an immunotherapy regimen.

The error here arises from the Examiner falling "into the hindsight trap." *In re Kotzab*, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000). As the Court stated in *Kotzab*, "... to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." *Id.* at 1316, *citing In re Dance*, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *In re Gordon*, 211 USPQ 1125, 1127 (Fed. Cir. 1984). The Antibody Patents teach methods to elicit antibodies to the immunizing agent, *e.g.*, a hapten-like compound such as an advanced glycosylation end-product (see the '704 patent, Exhibit 6). Geczy shows that haptenization results in hapten-specific immunity. Neither Murphy nor Berd 1989 suggest at least six administrations of the immunotherapeutic vaccine, much less the advantages of doing so disclosed in the Examples of the instant application. Thus, the Examiner has "... found prior art statements that in the abstract appeared to suggest the claimed limitation...", *Id.* at 1318, but which, in fact, lack any motivation to modify the teachings of Murphy or Berd 1989 to include that limitation.

With respect to the level of skill in the art, which the Examiner relies on in making this rejection (Final Office Action [Exhibit 2], page 4), Appellant respectfully submits that the Braun Declaration and the explicit teachings of the references show that the level of skill in the art does not supply the missing teaching here. *See A-Site Corp. v. VSI*, 50 USPQ2d 1161, 1171 (Fed. Cir. 1999). "[T]he level of skill in the art is a prism or lens through with a judge or jury

views the prior art and the claimed invention. This reference point prevents these deciders from using their own insight or, worse yet, hindsight, to gauge obviousness." *Id.* The Examiner has not established that the level of skill in the art is such that it would lead the skilled artisan to modify the teachings of Murphy or Berd 1989 as set forth in the claims. In particular, there is no incentive to administer vaccine six times (claims of Group C) or to treat non-melanoma tumors (claims of Group B). To rely on "conventional immunization schedules" is therefore in error.

The Examiner cited two cases to support her analysis of obviousness. In particular, the Examiner points out that "[t]he test for obviousness ... is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re Keller*, 208 USPQ 871, 881 (CCPA 1981) (Citations omitted). Appellant agrees, but points out that the Examiner must consider the references for all that they teach; it is impermissible to consider a reference in less than its entirety, or to disregard disclosures that diverge and teach away. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1993), *cert. denied* 469 U.S. 851 (1984). Such teaching away, which is the effect of the Antibody Patents and Geczy reference, defeats obviousness. See *Winner Int'l Royalty Corp. v. Wang*, 53 USPQ2d 1580, 1587 (Fed. Cir. 2000). Moreover, the prior art, and not the disclosure in the application, must both suggest the invention and provide a reasonable expectation of success in achieving it. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991).

Correctly applying the foregoing legal principles, the references neither (1) suggest the invention, nor (2) provide a reasonable expectation of success. With respect to the claims of Group C, Berd 1989 and, by extension, Murphy, are inadequate to suggest modifying the immunization strategy to require at least six administrations of an immunotherapeutic

vaccine. With respect to claim 76, the Examiner has not alleged any basis for rejecting a claim directed to treatment of tumors other than melanoma. Taken together, which as the Examiner has pointed out is how the references must be considered, the references do not render the claimed invention obvious. The Examiner's failure to properly consider the *Graham* factors, and the admitted use of hindsight to establish obviousness, represent error and should be reversed.

b. The rejection of claims 47, 65-72 and 74-77 over Berd 1989, the Antibody Patents, and Geczy

This rejection also pertains to the claims of Group C, with the exception of claim 76 (Group B). The Examiner maintained this rejection for the same reasons described in the above rejection. For the reasons set forth above, the combination of Berd 1989, the Antibody Patents, and Geczy, fails to render the instant invention obvious. Berd 1989, like Murphy, provides little to no information about method of treatment and therapeutic, which the Braun Declaration makes abundantly clear. In short, one of ordinary skill in the art would not have had any motivation to modify the teachings of Berd 1989 to require immunization with the haptenized tumor cell vaccine at least six times, and none of the cited references teaches treatment of non-melanoma tumors. The same reasons for separate patentability applies here as in the previous rejection. The Examiner has erroneously failed to establish the *Graham* factors sufficient to render the invention obvious, and instead has substituted hindsight to sustain this rejection, both of which constitute error. *See Ruiz*, 57 USPQ2d at 1167-68. Thus, this rejection is in error and should be reversed.

c. The rejection of claims 43, 44, 47, 49-62, 64-72, and 74-77 over Berd 1989, the Antibody Patents, and Geczy in view of Wiseman

This rejection pertains to claims in all of Groups A, B, and C. The broadest claim in Group A, claim 43, is directed to a composition comprising human tumor cells (other than melanoma cells) conjugated with a hapten. The tumor cells to be haptenized are obtained from the patient receiving treatment (*i.e.*, they are "autologous"), and are rendered incapable of growing in the body of a human before injection therein.

The broadest claim in Group B, claim 44, is directed to a method for treating a malignant tumor (other than melanoma) in a human patient by co-administering a composition comprising haptenized autologous human tumor cells of the same tumor type as the tumor in the patient, along with an adjuvant. The composition elicits at least one of the following upon administration to the patient with the adjuvant: an inflammatory immune response against the tumor of the patient; a delayed-type hypersensitivity response against the tumor of the patient; and activated T lymphocytes that infiltrate the tumor of the patient.

The broadest claim of Group C, claim 47, has been discussed above.

i. The Examiner's Reasoning

All references and the Examiner's reasons for combining them have been discussed above, except for Wiseman. The Examiner contends that "Wiseman clearly showed that autologous irradiated melanoma, lung, colon, and kidney cancer were successfully used for successful immunological treatment of those cancers and it would have been expected that these cell types, already known in the art to be useful as immunogenic cancer treatments would be

successfully substituted for the melanoma cells of Berd [1989] in order to treat the other cancer types." (Final Office Action [Exhibit 21, paragraph bridging pages 5 and 6).

ii. Appellant's arguments

The Braun Declaration addresses the teachings and deficiencies of the primary reference, ***Berd 1989***, as discussed above. Briefly, Berd 1989 lacks teachings with respect to any clinically significant tumor regression being observed, as well as the numbers and route of administration. (Braun Declaration [Exhibit 16], ¶¶ 9 and 11). Thus, one of ordinary skill in the art would have presumed that Berd 1989's haptenized tumor cells and BCG had been injected intra-tumorally, and that the BCG was thereby responsible for the observed, clinically non-significant, tumor responses (Braun Declaration [Exhibit 16],11). Accordingly, Berd 1989 suffers from a lack of expectation of success for the haptenized-tumor-cell approach in melanoma, and even more so in the case of non-melanoma tumors.

As discussed in the amendment dated September 22, 2000 (p. 17, 1't full paragraph), ***Wiseman*** teaches an alternative form of immunotherapy that depends on the route of administration: intralymphatic immunization. This alternative, which Wiseman indeed reports favorably, in no way suggests a deficiency or problem that would lead one of ordinary skill in the art to seek an alternative immunization strategy.

On the contrary, Wiseman diverts the skilled artisan away from the claimed invention, thus precluding combining this reference in making the rejection. One of ordinary skill in the art would, when provided with the Wiseman reference on one hand and Berd 1989 on the other, be inclined to pursue the Wiseman approach: intralymphatic immunization with

unmodified tumor cells, since this approach was successful and avoided the problems with the haptenization approach in Berd 1989. Finally, Geczy and the Antibody Patents lead away from any notion that haptenized tumor cells could yield an anti-tumor cell response, because they suggest an anti-hapten response, and, in addition, do not relate to cancer treatment. Such teaching away, which is the effect of the Antibody Patents and Geczy reference, defeats obviousness. *See Winner Int'l Royalty*, 53 USPQ2d at 1587.

As discussed above, nothing in Berd 1989 suggests that haptenization of tumor cells provides an effective therapeutic response (as established by the Braun Declaration), much less a more effective response than other immunization protocols. However, the data in the present specification clearly supports the unexpected superiority of the haptenized tumor cells and methods of immunotherapy using them.

> The DFS [disease-free survival] and TS [total survival] of [patients treated with haptenized tumor cells] were compared with those of 22 melanoma patients with resected nodal metastasises treated previously with unconjugated vaccine, see Example 4. Of 36 patients with stage 3 melanoma (palpable mass in one lymph node region), 22 are disease-free with a median follow-up of 33 months. Kaplan-Meir analysis projects a 3 year DFS and TS of 59% and 71 %, respectively. In contrast, the DFS and TS of stage 3 patients treated with unconjugated vaccine was 22% and 27% respectively ($p = 0.01$, log-rank test). Of 11 stage 4 patients (palpable mass in two lymph node regions), 5 are NED (no evidence of disease) with a median follow-up of 41 months.

(Specification, page 41, line 24 to page 42, line 8). These data demonstrate the superiority of the claimed invention, particularly the claimed methods of treatment, relative to Wiseman's approach.

These advantages, however, can only be gleaned from the disclosure of the specification, and are not available from the combined teachings of the references. Advantages

flowing directly from the invention are one consideration that may be relevant to a determination of obviousness. *Mosinee Paper Corp. v. James River Corp. of Virginia*, 22 U.S.P.Q.2d 1657, 1660, *aff'd. mem.* 980 F.2d 743 (Fed. Cir. 1992) (citing *Pre-Emption Devices, Inc. v. Minnesota Mining & Mfg. Co.*, 221 USPQ 841 (Fed. Cir. 1984)). "After all, those advantages are the foundation of that 'commercial success' which may be evidence of nonobviousness." *Pre-Emption, supra*, at 844 (*citing Graham*, 383 U.S. at 17). Thus, the showing of significant advantages of the presently claimed compositions and methods, particularly as related in Example 6 (quoted above), demonstrates non-obviousness of the invention.

Even if Berd 1989 ***had*** taught an effective immunotherapy of melanoma using haptenized, autologous melanoma cells, such a teaching would not form a sufficient basis for combination with Wiseman to achieve the claimed invention. As applicants have previously pointed out, it is not expected that "vaccines using other types of tumor cells, shown to effectively treat cancer, would behave in a mechanistically similar manner to the melanoma vaccine described in Berd et al." (See Paper No. 41 [Exhibit 3], page 5, lines 12-14). In the PTO-1449 form filed by Applicant on December 1, 1998, Applicant brought the Examiner's attention to Hanna et al. (U.S. Patent No. 5,484,596, hereinafter "Hanna"). Hanna teaches a method for the treatment of human colon cancer that involves the use of a vaccine which is made from irradiated human tumor cells. The Examiner was requested to note that the Hanna vaccine strategy appears to be effective only for treating colon cancer. A publication reporting on a clinical trial of the "Hanna" vaccine conceded that the vaccine was not effective for rectal cancer (Hoover et al., J. Clin. Oncology 11: 390-399, 1993; copy attached to the Amendment filed September 22, 2000 as Exhibit 1 [Exhibit 17], "Hoover"). Hoover states that ". . . no benefits were seen in patients with rectal cancer who received [active specific immunotherapy with an autologous tumor cell-BCG

vaccine]" (see Abstract; see also page 399, first column). Hence, even though the Hanna vaccine was reportedly successful in treating colon cancer, it failed to provide any benefits to patients with rectal cancer, a tumor type closely related to colon cancer. Accordingly, even had Berd 1989 successfully treated melanoma patients with his haptenized tumor cell vaccine, and not only provided preliminary and essentially anecdotal results relating to DTH-responses, it could not have been reasonably expected that a similar vaccine would be equally effective in the treatment of related tumors, much less tumors of completely unrelated origin.

It is clear that upon careful examination, the references cannot be combined as the Examiner has suggested. Thus, here the Examiner's citations appear on the surface to suggest the claimed invention, but, upon further review, can only be combined as the Examiner proposes with knowledge of the Applicant's invention. *In re Kotzab*, 55 USPQ2d at 1318. Such an analysis is, of course, improper. For the foregoing reasons, this obviousness rejection is in error and should be reversed.

iii. Separate Patentability Issues

The product claims of Group A cannot be obvious over the suggested combination of references, since the references cannot be combined to teach a haptenized non-melanoma tumor cell vaccine which elicits an anti-tumor response. Berd 1989 merely teaches a melanoma cell vaccine for immunotherapy, and Hanna and Hoover showed that an immunotherapy vaccine successful for one type of tumor would not function as a vaccine for another, closely related, tumor type. Thus, a combination with Geczy and the Antibody Patents and the Wiseman reference would not lead to any suggestion, much less conclusion, that the melanoma vaccine of Berd 1989 would indeed elicit an anti-tumor response if applied to wholly

unrelated tumor cells. Thus, there is no incentive from these references to haptenize non-melanoma tumor cells for an immunotherapy vaccine.

The method claims of Group B are not obvious over the suggested combination of references because (1) the references cannot be combined to teach a haptenized non-melanoma tumor cell vaccine which elicits an anti-tumor response; and (2) even when forcibly combined, they do not suggest a reasonable expectation of a successful treatment. The reasons why the references cannot be combined are provided in the preceding paragraph. As for the lack of expectation of success, Berd 1989, using haptenized melanoma cells, does not establish a successful immunotherapy method for melanoma. Geczy and the Antibody Patents suggest that an anti-hapten response would be the one and only result, and Wiseman proposes that intralymphatic injection of unmodified cells is a successful approach. Therefore, this combination of references, while admittedly raising expectations of success for the use of an ***unmodified*** tumor cell vaccine of Wiseman, could not possibly teach a reasonable expectation of success in achieving an anti-tumor response against a non-melanoma tumor using a haptenized vaccine.

Finally, the claims of Group C are not obvious over the (forced) combination of references simply because any administration schedule provided by the Antibody Patents to elicit a response to an antigen, exemplified by the "carrier"-associated glycosylation end-product of the `704 patent, would merely be applicable for eliciting an anti-hapten response, and not for an anti-tumor response, as previously described. These differences between the references except Wiseman and the Group C claims have been discussed. Wiseman adds nothing about an effective

number of administrations for a haptenized tumor cell vaccine. In short, the claims of Group C are patentable and distinct for all the reasons discussed in 8(a) and 8(b), *supra*.

Since the reasons for non-obviousness of the claims in the different claim groups are different, separate patentability considerations apply.

d. The rejection of claims 43, 44, 47, 49-62, 64-72, and 74-77 over Berd 1989, the Antibody Patents, Geczy, and Berd 1983

This rejection pertains to all of Groups A-C. The broadest claims of these claim groups, claims 43, 44, and 47, have been discussed above. The teachings of Berd 1989, the Antibody Patents, and Geczy have also been discussed above.

i. The Examiner's Reasoning

The Examiner contends that Berd 1983 teaches treatment of breast cancer patients with autologous vaccine, and that the substitution of the breast cancer cells of Berd 1983 for the melanoma cells of Berd 1989 was *prima facie* obvious. The Examiner also alleges that Appellant previously argued the Berd 1983 reference individually without clearly addressing the combined teachings.

Appellant respectfully disagrees. Appellant chose to, instead of repeating arguments already made in the amendment, discuss the entirety of the teachings of Berd 1983 before adding this reference to the combination of Berd 1989, the Antibody Patents, and Geczy (see amendment dated September 22, 2000, page 18, section 3.g). In doing so, it is clear that Berd 1983 adds nothing to the combination of Berd 1989, the Antibody Patents, and Geczy,

which combination is (1) improper and (2) fails to provide any reasonable expectation of success as discussed above.

ii. Applicant's Arguments

Berd 1983 teaches intradermal administration of autologous tumor cells to six cancer patients, five suffering from melanoma and one from breast cancer, and reports DTH responses against tumor cells in three out of the five evaluated patients. Note that Berd 1983 is silent with respect to whether the single breast cancer patient was among the 3 patients (50%) showing a DTH response. Even assuming that the breast cancer patient was among the three, the addition of Berd 1983 to the combination of reference would not provide a reasonable expectation that a haptenized tumor cell vaccine, whether based on melanoma or breast cancer cells, would elicit a clinically significant anti-tumor response.

The Braun Declaration addresses the teachings and deficiencies of ***Berd 1989***, as discussed above. The reference lacks teachings with respect to any clinically significant tumor regression being observed, as well as the numbers and route of administration. (Braun Declaration [Exhibit 16], ¶¶9 and 11). Thus, one of ordinary skill in the art would have presumed that Berd 1 989's haptenized tumor cells and BCG had been injected intratumorally, and that the BCG was thereby responsible for the observed, clinically non-significant, tumor responses (Braun Declaration [Exhibit 16], ¶11). Accordingly, Berd 1989 suffers from a lack of expectation of success for the haptenized-tumor-cell approach in melanoma, and even more so in the case of non-melanoma tumors.

As noted above, even if Berd 1989 taught an effective immunotherapy of melanoma using haptenized, autologous melanoma cells, such a teaching would not form a sufficient basis for combination with Berd 1983 to achieve the claimed invention. As applicants have previously pointed out, it is not expected that "vaccines using other types of tumor cells, shown to effectively treat cancer, would behave in a mechanistically similar manner to the melanoma vaccine described in Berd et al." (See Paper No. 41 [Exhibit 31, page 5, lines 12-14). As described in section 8.d.ii above, Appellant brought the Examiner's attention to Hanna and to Hoover [Exhibit 17], the latter of which showed that the "Hanna" vaccine, reportedly successful for treating colon cancer, was unsuccessful for treating rectal cancer. Hence, if a vaccine strategy cannot be successfully translated from colon cancer to rectal cancer, a person of skill could not reasonably expect to translate Berd 1989's melanoma cell vaccine to a successful, wholly unrelated, breast cancer or other non-melanoma vaccine.

iii. Separate Patentability Issues

The teachings of Berd 1983 are the same as those of Wiseman 1983 in the context of the Examiner's rejection discussed under section 8.d herein, and all other references are the same. Therefore, Groups A-C have different patentability considerations for the same reasons as those presented in section 8.d.iii above.

iv. Errors in Rejection

It is clear that upon careful examination, the references cannot be combined as the Examiner has suggested. Thus, even though the Examiner's citations appear on the surface to suggest the claimed invention, upon further review it is discovered that they can only be

combined as the Examiner proposes with knowledge of the Applicant's invention. ***In re Kotzab***, 55 USPQ2d at 1318. Such an analysis is, of course, improper. For the foregoing reasons, this obviousness rejection is in error and should be reversed.

e. The rejection of claims 43, 44, 47, 49-62, 64-72, and 74-77 over Bard, the Antibody Patents, Geczy, and Sanda and Moody

This rejection pertains to claims in all of Groups A-C. The broadest claims in these claim groups, claims 43, 44, and 47, have been discussed above. Berd, the Antibody Patents, and Geczy, as well as their teachings, are discussed above.

i. The Examiner's Reasons

The Examiner has stated that in particular Berd 1989 supplies the motivation to "decorate the tumor cells with hapten." Incorporating the reasoning set forth in the prior two Office Actions, the Examiner states that Moody teaches that lymphokine-transfected prostate cells generate an anti-tumor effect in vivo, and that Sanda addresses the feasibility of gene therapy for human prostate cancer. These references appear to be relevant to the Examiner because they suggest methods of anti-prostate cancer therapy.

ii. Applicant's Arguments

Sanda teaches a method for transducing human prostate cancer cells with a particular retroviral vector. This approach is wholly unrelated to any immunotherapy method for cancer treatment, and it solves a different problem (tumor cell ablation through a therapeutic gene) than the claimed invention (tumor cell immunotherapy using a haptenized tumor cell as a vaccine). Thus, there is no logical connection between Sanda and the other references cited in

this rejection. *See Ruiz*, 57 USPQ2d at 1168 (evidence that the references solve different problems can preclude a determination of obviousness).

Moody teaches an immunotherapy method based on transfection of rat prostate tumor cells to make them express the lymphokines IL-2 and IL-4. Although reportedly successful, the method disclosed in this reference adopts an altogether different approach than haptenization of tumor cells, and there is no suggestion from Moody to modify his approach by haptenization.[6]

In short, for the reasons discussed above, the forced combination of Berd 1989, the Antibody Patents, and Geczy fail to suggest, much less teach, compositions of haptenized non-melanoma tumor cells, methods of cancer immunotherapy using haptenized non-melanoma tumor cells, or methods of cancer immunotherapy involving a specific regimen of administering haptenized tumor cells at least six times. Sanda and Moody have nothing to do with such immunotherapy; they are in this respect less relevant than Wiseman. Accordingly, for the reasons advanced above, this rejection is in error and must be reversed.

iii. Separate Patentability Considerations

Sanda and Moody add nothing of relevance for any of Groups A-C, and the distinctions between the claims and all other references considered together are the same.

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[6] As disclosed in the specification of the instant application, using immunostimulatory molecules in combination, with the claimed compositions and methods may be desirable in some instances. (Specification, page 17, lines 17-20). Moody provides one avenue for such a combination. This in no way suggests the claimed invention.

Therefore, Groups A-C have different patentability considerations for the same reasons as those presented in section 8.d.iii above.

iv. Error's in Rejection

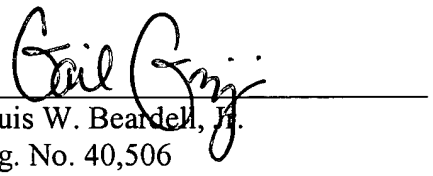
It is clear that upon careful examination, the references cannot be combined as the Examiner has suggested. Thus, even though the Examiner's citations appear on the surface to suggest the claimed invention, upon further review it is discovered that they can only be combined as the Examiner proposes with knowledge of the Applicant's invention. *In re Kotzab*, 55 USPQ2d at 1318. Such an analysis is, of course, improper. For the foregoing reasons, this obviousness rejection is in error and should be reversed.

9. Conclusion

For the forgoing reasons, Appellant submits that the Final Rejection is in error and should be reversed on all grounds. The Examiner has committed error by failing across the board to properly articulate the *Graham* factors. For example, Examiner did not properly consider the scope and content of the prior art, and the differences between the prior art and the claimed invention. *Ruiz*, 57 USPQ2d at 1167. The Examiner further failed to establish the level of ordinary skill in the art, *Id.* at 1168, which Appellant has established through the Braun Declaration as well as through the references. With respect to considering the scope and content of the prior art and the differences between the prior art and the claimed invention, the Examiner failed to articulate "... a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." *Id.* at 1167 (citations omitted). Instead, the Examiner has improperly relied on an arbitrary, non-existent level of skill

in the art to fill in the holes in the prior art, See A-Site Corp. 50 USPQ2d at 1171, and has consistently fallen into the "hindsight trap". *In re Kotzab*, 55 USPQ2d at 1318. For these reasons, reversal of all rejections and remand of the application for allowance is believed to be in order and is earnestly solicited.

Respectfully submitted,



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APPENDIX

Pending Claims on Appeal

44. (Amended) A composition comprising human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein;

said composition eliciting, when administered together with an adjuvant, an inflammatory immune response against the tumor of said patient, wherein said tumor is not melanoma.

45. A method for treating a malignant tumor in a human patient comprising co-administering to the patient

(a) a composition comprising a therapeutically effective amount of human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein; and

(b) an adjuvant;

wherein said composition elicits at least one of the following upon administration to said patient with the adjuvant: an inflammatory immune response against the tumor of said patient; a delayed-type hypersensitivity response against the tumor of said patient, and activated T lymphocytes that infiltrate the tumor of said patient, wherein said malignant tumor is not melanoma.

46. (Amended) A method of treating a malignant tumor in a human patient comprising co-administering to the patient

(a) a composition comprising a therapeutically effective amount of human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein; and

(b) an adjuvant;

wherein said composition elicits at least one of the following upon administration to said patient with the adjuvant: an inflammatory immune response against the tumor of said patient; a delayed-type hypersensitivity response against the tumor of said patient and activated T lymphocytes that infiltrate the tumor of said patient; and

repeating said administration at least six times at spaced apart intervals.

49. The composition of claim 43 wherein said tumor cells are selected from lung, colon, breast, kidney, and prostate tumor cells.

50. The composition of claim 43 wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5 sylfonic 1 -naphtyl) ethylene diamine.

51. The composition of claim 43 wherein said hapten is dinitrophenyl.

52. The composition of claim 43 further comprising an adjuvant.

53. The composition of claim 52 wherein said adjuvant is Bacillus Cal mette-Guerin.

54. The composition of claim 43 further comprising a carrier.

55. The composition of claim 54 wherein said carrier is selected from the group consisting of saline solution and culture medium.

56. The method of claim 44 wherein said tumor cells are selected from lung, colon, breast, kidney, and prostate tumor cells.

57. The method of claim 44, wherein said malignant tumor is from a cancer selected from the group consisting of lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer.

58. The method of claim 44 wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5-sulfonic 1 -naphtyl) ethylene diamine.

59. The method of claim 44 wherein said hapten is dinitrophenyl.

60. The method of claim 44 further comprising administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition.

61. The method of claim 60 wherein said therapeutically effective amount of cyclophosphamide comprises administering a dose of about 300 mg/M2 of cyclophosphamide prior to administration of said composition.

62. The method of claim 60 further comprising sensitizing the patient with a therapeutically effective amount of 1-fluoro-2,4-dinitrobenzene prior to administering cyclophosphamide.

64. The method of claim 44 wherein said adjuvant is Bacillus Calmette-Guerin.

65. The method of claim 47 wherein said tumor cells are selected from melanoma, lung, colon, breast, kidney, and prostate tumor cells.

66. The method of claim 47, wherein said malignant tumor is from a cancer selected from the group consisting of melanoma cancer, lung cancer, colon cancer, breast cancer, kidney cancer, and prostate cancer.

67. The method of claim 47 wherein said hapten is selected from the group consisting of dinitrophenyl, trinitrophenyl, and N-iodoacetyl-N'-(5-sulfonic 1 -naphtyl) ethylene diamine.

68. The method of claim 47 wherein said hapten is dinitrophenyl.

69. The method of claim 47 further comprising administering a therapeutically effective amount of cyclophosphamide prior to administration of said composition.

70. The method of claim 47, further comprising administering a therapeutically effective amount of cyclophosphamide prior to the first administration of said composition.

71. The method of claim 69 wherein said therapeutically effective amount of cyclophosphamide comprises administering a dose of about 300 mg/M2 of cyclophosphamide prior to administration of said composition.

72. The method of claim 47 further comprising sensitizing the patient with a therapeutically effective amount of 1 -fluoro-2,4-dinitrobenzene prior to administering cyclophosphamide.

74. The method of claim 47 wherein said adjuvant is Bacillus Calmette-Guerin.

75. The method of claim 47 wherein said administration prolongs survival of said patient.

76. The method of claim 44, wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8 + CD4.

77. The method of claim 47, wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly CD8 + CD4.

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Name: Gail H. Griffin Signature: _____

Dated: August 28, 2006